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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,726	11/19/2001	Avi J. Ashkenazi	P2730P1C60	9979

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HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CO 94025-3506

EXAMINER	
LANDSMAN, ROBERT S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,726	GENENTECH, INC.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/24/02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Comparisons* A+B

DETAILED ACTION

1. Formal Matters

A. The Preliminary Amendment dated 11/19/01, has been entered into the record.

B. Claims 119-138 are pending and are the subject of this Office Action.

2. Priority

Due to the excessive number of applications from which the present application claims benefit, priority cannot be determined. However, the Examiner has concluded that the subject matter defined in this application is not supported by any of the applications in the chain of priority because the presently claimed subject matter is not supported by a specific, substantial or well-established utility, nor, for this reason, is it enabled. Accordingly, the subject matter defined in claims 119-138 has an effective filing date of 11/19/01, which is the filing date of the present application.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 11/19/01 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to 11/19/01.

3. Information Disclosure Statement

A. References A1 and A2 on the IDS dated 5/24/02 have been lined through since they are not in proper format, including author and date of deposit.

4. Specification

A. Though none could be found, due to the length of the specification, Applicants are reminded that embedded hyperlink and/or other form of browser-executable code are not permitted in the specification. See MPEP § 608.01.

B. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title recites polypeptides and polynucleotides whereas the claims are drawn to polynucleotides.

5. Claim Objections

A. The syntax of claims 119-138 could be improved by replacing the phrase "shown in Figure 233 (SEQ ID NO:326)" with "of SEQ ID NO:326" and "shown in Figure 232 (SEQ ID NO:325)" with "of SEQ ID NO:325" where approproiate.

6. Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A. Claims 119-138 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility. These claims are directed to polynucleotides having various sequence homology to SEQ ID NO:325, or encoding SEQ ID NO:326. However, the invention encompassed by these claims has no apparent or disclosed patentable utility. This rejection is consistent with the current utility guidelines, published 1/5/01, 66 FR 1092. The instant application has provided a description of an isolated protein and its encoding polynucleotide. However, the instant application does not disclose a specific and substantial biological role of this protein or its significance.

However, it is clear from the instant specification that the claimed protein is what is termed an "orphan receptor" in the art. The instant application does not disclose the biological role of the claimed protein or its significance. Applicants disclose in the specification that the receptor is a secreted protein. However, this fact, alone, is insufficient to confer utility to the protein of the present invention. Therefore, the instant claims are drawn to a polynucleotide encoding a protein which has a yet undetermined function or biological significance. There is no actual and specific significance which can be attributed to said protein identified in the specification. For this reason, the instant invention is incomplete. In the absence of a knowledge of the natural ligands or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which bind to and/or mediate activity of the said receptor is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real-world" use for said protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. 101 as being useful.

Furthermore, since the protein of the invention is not supported by a specific and substantial asserted utility or a well established utility, the encoding polynucleotides, vectors, host cells and methods of making the protein also lack utility.

7. Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 119-138 are rejected under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to use the instant invention. Specifically, since the claimed invention is not supported by a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

B. Claims 119-138 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of the biological material is considered necessary for the enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R. §§ 1.801-1.809). Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If a deposit (203129) is made under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g. see 961 OG 21, 1977), and Applicants, their assignee or their agent needs to provide a declaration containing the following:

1. the current address of the ATCC.
2. a declaration, or statement over attorney's signature stating that all restrictions imposed by the depositor on the availability to the public of the deposited biological material be irrevocably removed upon the granting of the patent (see MPEP Chapter 2410.01 and 37 C.F.R. § 1.808.

C. Furthermore, even if the claims possessed utility under 35 USC 101, claims 119-138 would still be rejected under 35 USC 112, first paragraph, because the specification, while then being enabling for SEQ ID NO:325 and 326, does not reasonably provide enablement for polynucleotides or polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to SEQ ID NO:325 or 326, to the protein

encoded by ATCC No. 203129, for the extracellular domain thereof, or for vectors and host cells containing these polynucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. There is no functional limitation in the claims. The claims encompass an unreasonable number of inoperative polypeptides, or polynucleotides which encode these polypeptides, which the skilled artisan would not know how to use.

There are no working examples of polynucleotides or polypeptides less than 100% identical to SEQ ID NO:325 or 326, or the mature form thereof (i.e. lacking its signal peptide). The skilled artisan would not know how to use non-identical polypeptides or polynucleotides on the basis of teachings in the prior art or specification unless they possessed a specific function disclosed in the instant specification, in which there is none. While the specification generally describes homologous proteins, Applicants still have not taught to which family of proteins the protein of the present invention belongs. The specification does not provide guidance for using polynucleotides encoding polypeptides related to (*i.e.*, 80%-99% identity) but not identical to SEQ ID NO:325 or 326 which do not have any specific, known function. The claims are broad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of proteines and lack of knowledge about function(s) of encompassed polypeptides structurally related to SEQ ID NO:326, or their encoding polynucleotides (e.g. SEQ ID NO:325) the lack of direction or guidance for using polypeptides that are not identical to SEQ ID NO:326, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

8. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 119-138 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polynucleotides having at least 80%, 85%, 90%, 95% or 99% sequence identity with SEQ ID NO:325 as well as vectors and host cells. The claims do not require that the polynucleotides or encoded polypeptides of the present invention possess any particular biological

activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:314, or encoded by SEQ ID NO:325, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

9. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 119-138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 119-138 are vague and indefinite since it is not clear whether or not the protein encoded by the polynucleotide of the present invention is a soluble protein (e.g protease), nor is it disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed protein comprises an "extracellular domain" is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain"..."lacking its associated signal sequence" is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

B. Claims 132-134 are vague and indefinite since the claim recites "hybridizes" without the recitation of any conditions, or recites "stringent conditions: wherein these conditions are not known. Nucleic acid molecules which hybridize under conditions of "low" stringency would not necessarily hybridize under conditions of "high" stringency. Furthermore, not all conditions of "high" or "low" stringency, for example, are the same. Therefore, it is required that Applicants amend the claims to recite the exact hybridization conditions without using indefinite phrases such as "*for example*" **without adding new matter**.

10. Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Claims 119-138 are rejected under 35 U.S.C. 102(b) as being anticipated by Baker et al. (WO 99/63088. The claims recite a polynucleotide at least 80% identical to that of SEQ ID NO: 325 or encoding 326, as well as fragments thereof. The claims also recite nucleic acid molecules which hybridize

to SEQ ID NO:325, or one encoding SEQ ID NO:326 as well as vectors and host cells. Baker teach a polynucleotide which is 100% identical to SEQ ID NO:325 (Sequence Comparisons A and B) as well as vectors and host cells (pages 352-355). This nucleic acid molecule will hybridize to that of the present invention even under the most stringent conditions.

11. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
March 05, 2004

ROBERT LANDSMAN
PATENT EXAMINER

Sequence Comparison A

SEQ ID NO:325

ID AAZ65074 standard; cDNA; 2988 BP.
XX
AC AAZ65074;
XX
DT 05-APR-2000 (first entry)
XX
DE Membrane-bound protein PRO1281 encoding cDNA.
XX
KW Membrane-bound polypeptide; PRO polypeptide; LDL receptor; TIE ligand;
KW pharmaceutical; receptor immunoadhesin; gene mapping; ss.
XX
OS Homo sapiens.
XX
PN WO9963088-A2.
XX
PD 09-DEC-1999.
XX
PF 02-JUN-1999; 99WO-US12252.
XX
PA (GETH) GENENTECH INC.
XX
PI Baker K, Chen J, Goddard A, Gurney AL, Smith V, Watanabe CK;
PI Wood WI, Yuan J;
XX
DR WPI; 2000-072883/06.
DR P-PSDB; AAY66729.
XX
PT Membrane-bound proteins and related nucleotide sequences -
XX
PS Claim 2; Fig 232; 822pp; English.
XX
CC The invention provides membrane-bound PRO polypeptides and
CC polynucleotides encoding them. The PRO sequences of the invention were
CC identified based on extracellular domain homology screening. The PRO
CC sequences have homology with proteins including LDL receptors, TIE
CC ligands and various enzymes. The membrane-bound proteins and receptor
CC molecules are useful as pharmaceutical and diagnostic agents. Receptor
CC immunoadhesins, for instance, can be used as therapeutic agents to block
CC receptor-ligand interactions. The membrane-bound proteins can also be
CC employed for screening of potential peptide or small molecule inhibitors
CC of the relevant receptor/ligand interaction. The PRO encoding sequences
CC are useful as hybridization probes, in chromosome and gene mapping and in
CC the generation of antisense RNA and DNA. PRO nucleic acid sequences
CC will also be useful for the preparation of PRO polypeptides, especially
CC by recombinant techniques.
XX
SQ Sequence 2988 BP; 464 A; 1059 C; 962 G; 503 T; 0 other;

Query Match 100.0%; Score 2988; DB 21; Length 2988;
Best Local Similarity 100.0%; Pred. No. 0;
Matches 2988; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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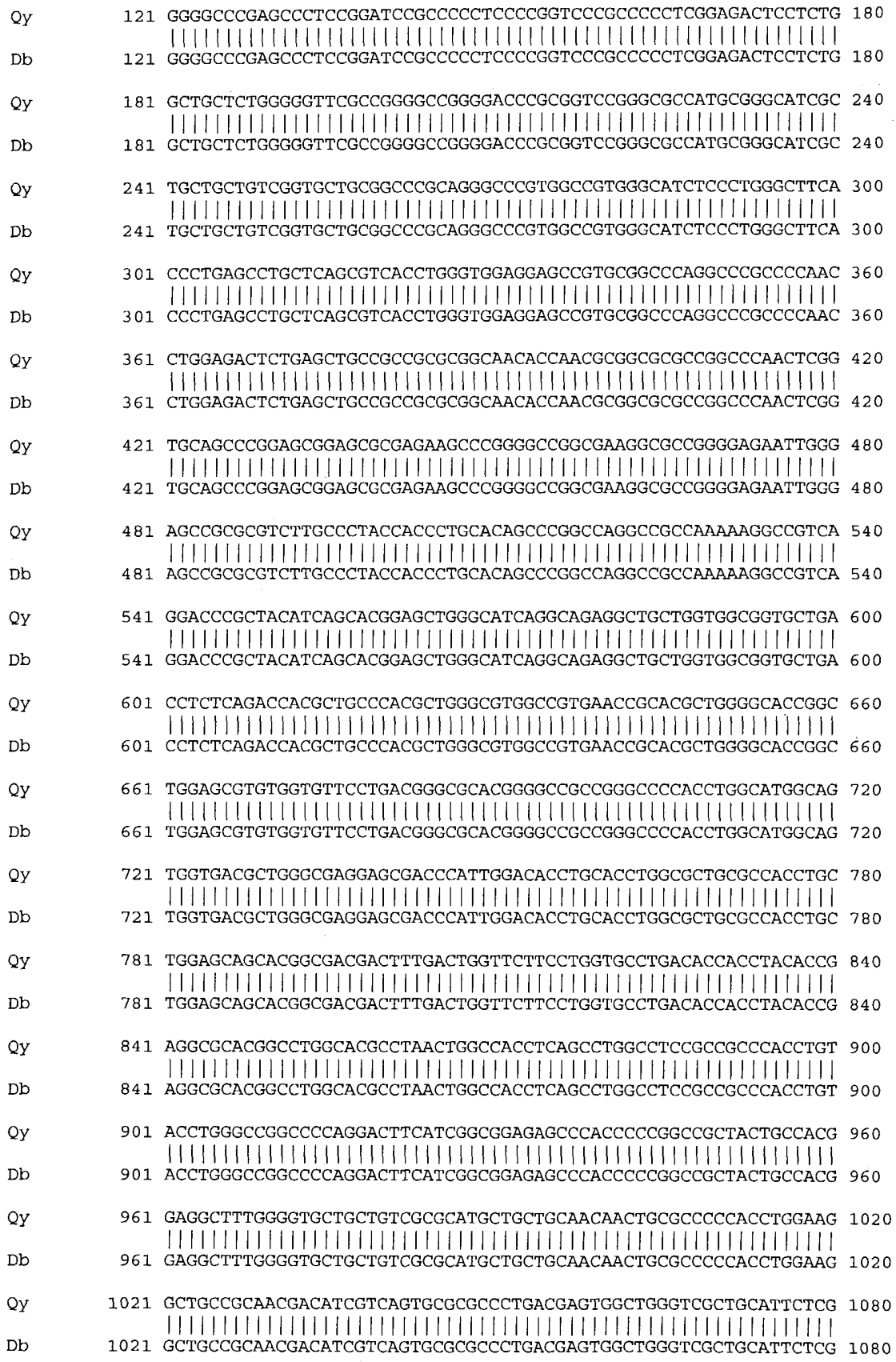

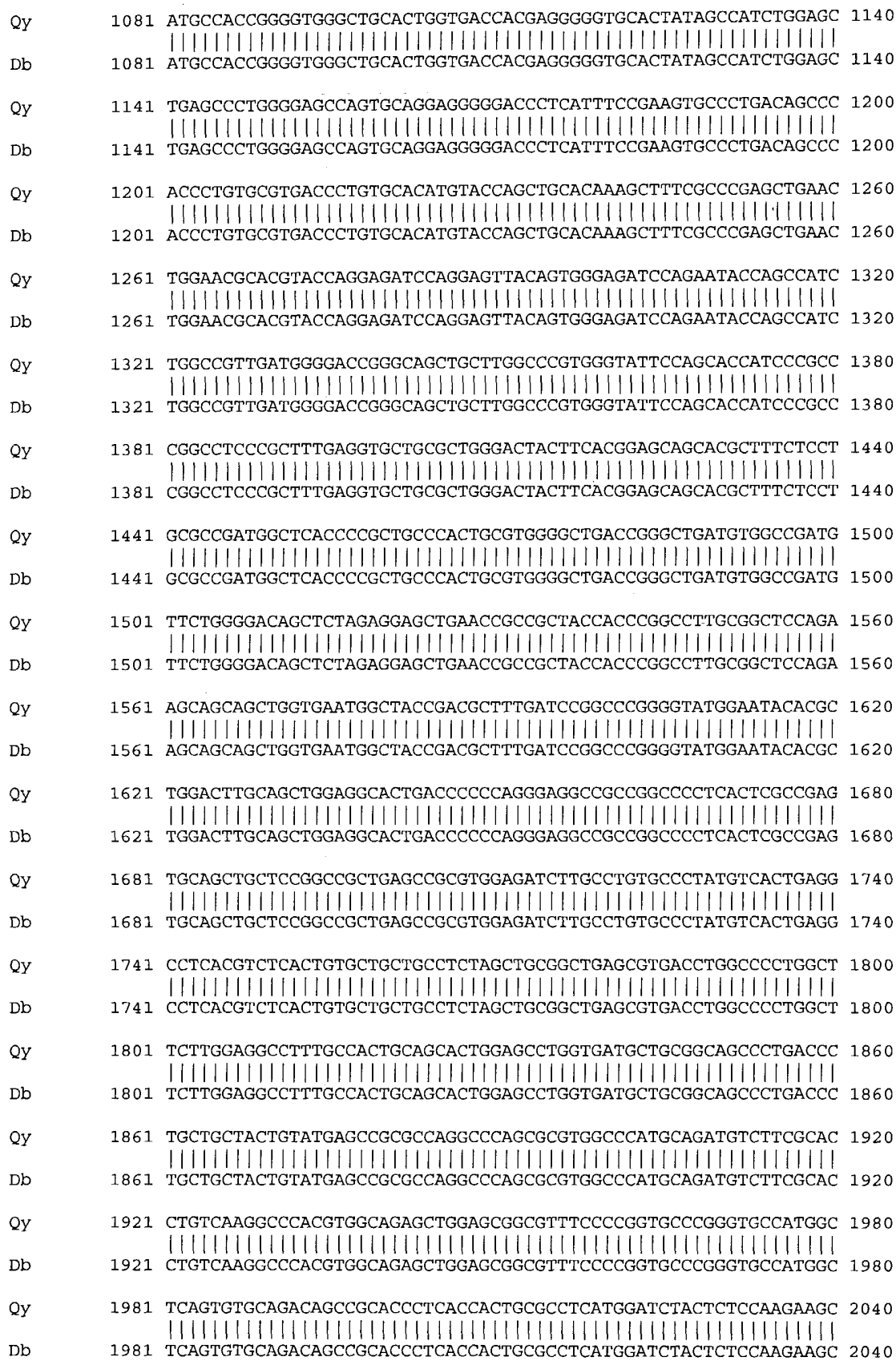
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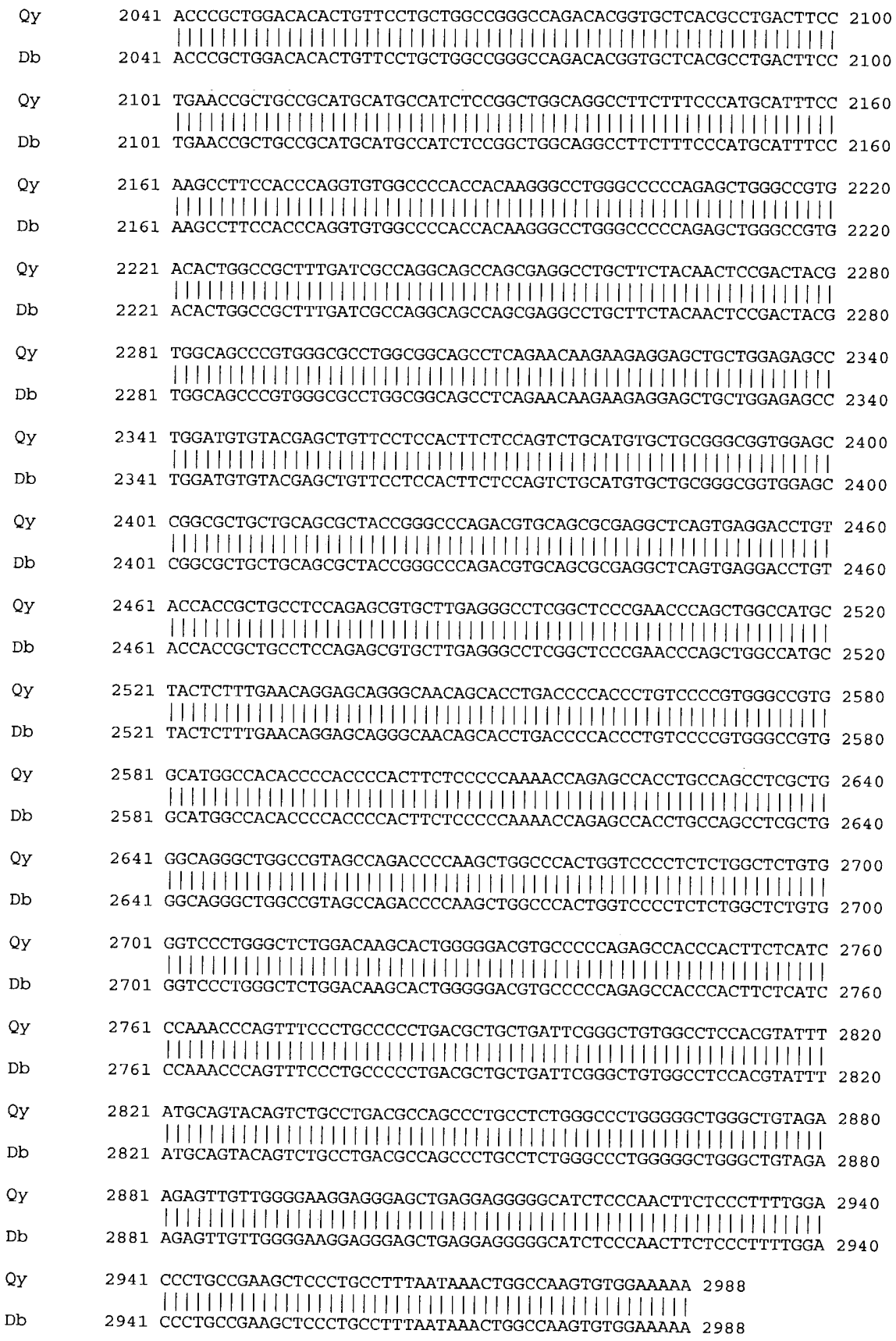
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Qy 2761 CCAAACCCAGTTTCCCTGCCCCCTGACGCTGCTGATTCGGGCTGTGGCCTCCACGTATTT 2820
Db 2761 CCAAACCCAGTTTCCCTGCCCCCTGACGCTGCTGATTCGGGCTGTGGCCTCCACGTATTT 2820
Qy 2821 ATGCAGTACAGTCTGCCTGACGCCAGCCCTGCCTCTGGGCCCTGGGGGCTGGGCTGTAGA 2880
Db 2821 ATGCAGTACAGTCTGCCTGACGCCAGCCCTGCCTCTGGGCCCTGGGGGCTGGGCTGTAGA 2880
Qy 2881 AGAGTTGTTGGGGAAGGAGGGAGCTGAGGAGGGGGCATCTCCCAACTTCTCCCTTTTGGA 2940
Db 2881 AGAGTTGTTGGGGAAGGAGGGAGCTGAGGAGGGGGCATCTCCCAACTTCTCCCTTTTGGA 2940
Qy 2941 CCCTGCCGAAGCTCCCTGCCTTTAATAAACTGGCCAAGTGTGGAAAAA 2988
Db 2941 CCCTGCCGAAGCTCCCTGCCTTTAATAAACTGGCCAAGTGTGGAAAAA 2988

Sequence Comparison B

B

SEQ ID NO:326 with DNA

PN WO9963088-A2.
XX
PD 09-DEC-1999.
XX
Alignment Scores:

Pred. No.:	2.74e-224	Length:	2988
Score:	4074.00	Matches:	775
Percent Similarity:	100.00%	Conservative:	0
Best Local Similarity:	100.00%	Mismatches:	0
Query Match:	100.00%	Indels:	0
DB:	21	Gaps:	0

US-09-989-726-326 (1-775) x AAZ65074 (1-2988)

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Qy          1 MetArgAlaSerLeuLeuLeuSerValLeuArgProAlaGlyProValAlaValGlyIle 20
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        228 ATGCGGGCATCGCTGCTGCTGTCGGTGCTGCGGCCCGCAGGGCCCGTGGCCGTGGGCATC 287

Qy         21 SerLeuGlyPheThrLeuSerLeuLeuSerValThrTrpValGluGluProCysGlyPro 40
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        288 TCCCTGGGCTTCACCCTGAGCCTGCTCAGCGTCACCTGGGTGGAGGAGCCGTGCGGCCCA 347

Qy         41 GlyProProGlnProGlyAspSerGluLeuProProArgGlyAsnThrAsnAlaAlaArg 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        348 GGCCCGCCCCAACCTGGAGACTCTGAGCTGCCGCCGCGCGGCAACACCAACGCGGCGCGC 407

Qy         61 ArgProAsnSerValGlnProGlyAlaGluArgGluLysProGlyAlaGlyGluGlyAla 80
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        408 CGGCCCAACTCGGTGCAGCCCGGAGCGGAGCGCGAGAAGCCCGGGGCCGGCGAAGGCGCC 467

Qy         81 GlyGluAsnTrpGluProArgValLeuProTyrHisProAlaGlnProGlyGlnAlaAla 100
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        468 GGGGAGAATTGGGAGCCGCGCGTCTTGCCCTACCACCCTGCACAGCCCGGCCAGGCCGCC 527

Qy        101 LysLysAlaValArgThrArgTyrIleSerThrGluLeuGlyIleArgGlnArgLeuLeu 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        528 AAAAAGGCCGTCAGGACCCGCTACATCAGCACGGAGCTGGGCATCAGGCAGAGGCTGCTG 587

Qy        121 ValAlaValLeuThrSerGlnThrThrLeuProThrLeuGlyValAlaValAsnArgThr 140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        588 GTGGCGGTGCTGACCTCTCAGACCACGCTGCCCACGCTGGGCGTGGCCGTGAACCGCACG 647

Qy        141 LeuGlyHisArgLeuGluArgValValPheLeuThrGlyAlaArgGlyArgArgAlaPro 160
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        648 CTGGGGCACCGGCTGGAGCGTGTGGTGTTCCTGACGGGCGCACGGGGCCGCCGGGCCCCA 707

Qy        161 ProGlyMetAlaValValThrLeuGlyGluGluArgProIleGlyHisLeuHisLeuAla 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        708 CCTGGCATGGCAGTGGTGACGCTGGGCGAGGAGCGACCCATTGGACACCTGCACCTGGCG 767

Qy        181 LeuArgHisLeuLeuGluGlnHisGlyAspAspPheAspTrpPhePheLeuValProAsp 200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        768 CTGCGCCACCTGCTGGAGCAGCACGGCGACGACTTTGACTGGTTCTTCCTGGTGCCTGAC 827

Qy        201 ThrThrTyrThrGluAlaHisGlyLeuAlaArgLeuThrGlyHisLeuSerLeuAlaSer 220
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        828 ACCACCTACACCGAGGCGCACGGCCTGGCACGCCTAACTGGCCACCTCAGCCTGGCCTCC 887

Qy        221 AlaAlaHisLeuTyrLeuGlyArgProGlnAspPheIleGlyGlyGluProThrProGly 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        888 GCCGCCCACCTGTACCTGGGCCGGCCCCAGGACTTCATCGGCGGAGAGCCCACCCCCGGC 947
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Qy        241 ArgTyrCysHisGlyGlyPheGlyValLeuLeuSerArgMetLeuLeuGlnGlnLeuArg 260
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        948 CGCTACTGCCACGGAGGCTTTGGGGTGCTGCTGTCGCGCATGCTGCTGCAACAACTGCGC 1007

Qy        261 ProHisLeuGluGlyCysArgAsnAspIleValSerAlaArgProAspGluTrpLeuGly 280
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1008 CCCCACCTGGAAGGCTGCCGCAACGACATCGTCAGTGCGCGCCCTGACGAGTGGCTGGGT 1067

Qy        281 ArgCysIleLeuAspAlaThrGlyValGlyCysThrGlyAspHisGluGlyValHisTyr 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1068 CGCTGCATTCTCGATGCCACCGGGGTGGGCTGCACTGGTGACCACGAGGGGGTGCACTAT 1127

Qy        301 SerHisLeuGluLeuSerProGlyGluProValGlnGluGlyAspProHisPheArgSer 320
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1128 AGCCATCTGGAGCTGAGCCCTGGGGAGCCAGTGCAGGAGGGGGACCCTCATTTCCGAAGT 1187

Qy        321 AlaLeuThrAlaHisProValArgAspProValHisMetTyrGlnLeuHisLysAlaPhe 340
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1188 GCCCTGACAGCCCACCCTGTGCGTGACCCTGTGCACATGTACCAGCTGCACAAAGCTTTC 1247

Qy        341 AlaArgAlaGluLeuGluArgThrTyrGlnGluIleGlnGluLeuGlnTrpGluIleGln 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1248 GCCCGAGCTGAACTGGAACGCACGTACCAGGAGATCCAGGAGTTACAGTGGGAGATCCAG 1307

Qy        361 AsnThrSerHisLeuAlaValAspGlyAspArgAlaAlaAlaTrpProValGlyIlePro 380
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1308 AATACCAGCCATCTGGCCGTTGATGGGGACCGGGCAGCTGCTTGGCCCGTGGGTATTCCA 1367

Qy        381 AlaProSerArgProAlaSerArgPheGluValLeuArgTrpAspTyrPheThrGluGln 400
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1368 GCACCATCCCGCCCGGCCTCCCGCTTTGAGGTGCTGCGCTGGGACTACTTCACGGAGCAG 1427

Qy        401 HisAlaPheSerCysAlaAspGlySerProArgCysProLeuArgGlyAlaAspArgAla 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1428 CACGCTTTCTCCTGCGCCGATGGCTCACCCCGCTGCCCACTGCGTGGGGCTGACCGGGCT 1487

Qy        421 AspValAlaAspValLeuGlyThrAlaLeuGluGluLeuAsnArgArgTyrHisProAla 440
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1488 GATGTGGCCGATGTTCTGGGGACAGCTCTAGAGGAGCTGAACCGCCGCTACCACCCGGCC 1547

Qy        441 LeuArgLeuGlnLysGlnGlnLeuValAsnGlyTyrArgArgPheAspProAlaArgGly 460
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1548 TTGCGGCTCCAGAAGCAGCAGCTGGTGAATGGCTACCGACGCTTTGATCCGGCCCGGGGT 1607

Qy        461 MetGluTyrThrLeuAspLeuGlnLeuGluAlaLeuThrProGlnGlyGlyArgArgPro 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1608 ATGGAATACACGCTGGACTTGCAGCTGGAGGCACTGACCCCCCAGGGAGGCCGCCGGCCC 1667

Qy        481 LeuThrArgArgValGlnLeuLeuArgProLeuSerArgValGluIleLeuProValPro 500
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1668 CTCACTCGCCGAGTGCAGCTGCTCCGGCCGCTGAGCCGCGTGGAGATCTTGCCTGTGCCC 1727

Qy        501 TyrValThrGluAlaSerArgLeuThrValLeuLeuProLeuAlaAlaAlaGluArgAsp 520
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1728 TATGTCACTGAGGCCTCACGTCTCACTGTGCTGCTGCCTCTAGCTGCGGCTGAGCGTGAC 1787

Qy        521 LeuAlaProGlyPheLeuGluAlaPheAlaThrAlaAlaLeuGluProGlyAspAlaAla 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1788 CTGGCCCCTGGCTTCTTGGAGGCCTTTGCCACTGCAGCACTGGAGCCTGGTGATGCTGCG 1847

Qy        541 AlaAlaLeuThrLeuLeuLeuLeuTyrGluProArgGlnAlaGlnArgValAlaHisAla 560
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1848 GCAGCCCTGACCCTGCTGCTACTGTATGAGCCGCGCCAGGCCCAGCGCGTGGCCCATGCA 1907
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Qy        561 AspValPheAlaProValLysAlaHisValAlaGluLeuGluArgArgPheProGlyAla 580
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1908 GATGTCTTCGCACCTGTCAAGGCCCACGTGGCAGAGCTGGAGCGGCGTTTCCCCGGTGCC 1967

Qy        581 ArgValProTrpLeuSerValGlnThrAlaAlaProSerProLeuArgLeuMetAspLeu 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1968 CGGGTGCCATGGCTCAGTGTGCAGACAGCCGCACCCTCACCACTGCGCCTCATGGATCTA 2027

Qy        601 LeuSerLysLysHisProLeuAspThrLeuPheLeuLeuAlaGlyProAspThrValLeu 620
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2028 CTCTCCAAGAAGCACCCGCTGGACACACTGTTCCTGCTGGCCGGGCCAGACACGGTGCTC 2087

Qy        621 ThrProAspPheLeuAsnArgCysArgMetHisAlaIleSerGlyTrpGlnAlaPhePhe 640
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2088 ACGCCTGACTTCCTGAACCGCTGCCGCATGCATGCCATCTCCGGCTGGCAGGCCTTCTTT 2147

Qy        641 ProMetHisPheGlnAlaPheHisProGlyValAlaProProGlnGlyProGlyProPro 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2148 CCCATGCATTTCCAAGCCTTCCACCCAGGTGTGGCCCCACCACAAGGGCCTGGGCCCCCA 2207

Qy        661 GluLeuGlyArgAspThrGlyArgPheAspArgGlnAlaAlaSerGluAlaCysPheTyr 680
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2208 GAGCTGGGCCGTGACACTGGCCGCTTTGATCGCCAGGCAGCCAGCGAGGCCTGCTTCTAC 2267

Qy        681 AsnSerAspTyrValAlaAlaArgGlyArgLeuAlaAlaAlaSerGluGlnGluGluGlu 700
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2268 AACTCCGACTACGTGGCAGCCCGTGGGCGCCTGGCGGCAGCCTCAGAACAAGAAGAGGAG 2327

Qy        701 LeuLeuGluSerLeuAspValTyrGluLeuPheLeuHisPheSerSerLeuHisValLeu 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2328 CTGCTGGAGAGCCTGGATGTGTACGAGCTGTTCCTCCACTTCTCCAGTCTGCATGTGCTG 2387

Qy        721 ArgAlaValGluProAlaLeuLeuGlnArgTyrArgAlaGlnThrCysSerAlaArgLeu 740
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2388 CGGGCGGTGGAGCCGGCGCTGCTGCAGCGCTACCGGGCCCAGACGTGCAGCGCGAGGCTC 2447

Qy        741 SerGluAspLeuTyrHisArgCysLeuGlnSerValLeuGluGlyLeuGlySerArgThr 760
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2448 AGTGAGGACCTGTACCACCGCTGCCTCCAGAGCGTGCTTGAGGGCCTCGGCTCCCGAACC 2507

Qy        761 GlnLeuAlaMetLeuLeuPheGluGlnGluGlnGlyAsnSerThr 775
              |||||||||||||||||||||||||||||||||||||||||||||
Db       2508 CAGCTGGCCATGCTACTCTTTGAACAGGAGCAGGGCAACAGCACC 2552
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